A New Approach to Assess Drug Development Performance

A NEW APPROACH TO ASSESS DRUG DEVELOPMENT PERFORMANCE

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ABSTRACT

This article suggests that successful innovation in biopharmaceuticals is strongly related to the ability of firms to move forward compounds along the drug pipeline, relatively to other companies, within the same therapeutic area. We used this intuition to build indicators of performance at the firm-level and use them to conduct empirical analysis that relies upon a comprehensive database. We consider the effect of various factors on drug development performance, including R&D funds allocation across therapeutic areas and the proportion of biological molecules in the drug development portfolio. Subsequently, we show that a correlation exists between our performance variables and the per-capita growth of biopharmaceutical firms' revenues.

Key Words: Innovation, Pharmaceutical Firms, Portfolio Performance; R&D Productivity.

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1. INTRODUCTION

Over the last two decades empirical evidence indicates that R&D expenditures have substantially increased in the pharmaceutical industry [1] [2] [3] [4] [5]. However, such increase has not been matched by a proportional growth in R&D outputs, notably in terms of newly filed applications to test a drug candidate and/or new drug approvals. Though with qualifications, [1] [4], a consensus seems to have emerged that we are facing a productivity crisis.

The underlying reasons for this trend are at the centre of an open debate. Some analysts question whether decline in productivity is reality or fiction [1], [6]. Many studies attempt to identify and quantify the factors affecting innovation and R&D productivity rates in order to envisage possible remedies [2] [4] [7] [8]. Such factors include the growing complexity of discovery/research activities [9][10], the role of the regulatory framework [11] [12] and the consequences of organizational change [10] [13] [14] [3].

This literature encompasses a mix of case studies and quantitative analyses with the latter witnessing a proliferation of measures of innovative performance. Some of them rely on inputs to the innovation process (R&D investment, number of employees dedicated to R&D). However, a growing number of alternative approaches concentrate on innovation outputs, such as patent counts, the number of new therapies completing clinical development [13], [15] or reaching the market within a given time period [4] [16], [17], [18], the probability of moving a compound across clinical phases [12], the combination of cost and time required to develop a new therapy [2].

We propose to measure the drug development performance of biopharmaceutical companies by comparing actual firm performance at advancing drugs through the development pipeline against average past performance of drugs in the same therapeutic area. We test this performance measure by examining the relationship between revenue growth per capita and normalised performance indices derived from this method. We find that biopharmaceutical firms that outperform the industry's average had greater revenue growth; furthermore this ability depends on a variety of factors, including R&D funds allocation across therapeutic areas and the proportion of biological molecules in the drug development portfolio.

2. MOTIVATION AND APPROACH

Pipeline's structure represents a key strategic asset for organizations engaged in drug development, be they large pharmaceutical corporations (PCs), biopharmaceutical firms or public labs. Various factors contribute to determine the degree of a firm's success in terms of drugs that are developed, registered and commercialized.

Firstly, the higher such number the more likely it is for a portfolio to register one drug or more. Secondly, the development phase of compounds is also a crucial aspect; the closer a compound is to the registration phase the more likely its final approval and future commercialization. Therefore, in principle, the higher the number of molecules near to registration the more probable and closer in time is portfolio success. But since such late-stage compounds are more expensive to process than those farther from registration, resource constraints could raise opportunity cost issues and care must be taken to allocate available resources to the most promising compounds. Finally, if achieving drug registration is a landmark of portfolio success, the therapeutic area of the drug is also crucially important; not only are therapeutic areas characterised by different attrition rates [5], but also the economic value of a drug depends on its potential market demand and so achieving registration in a high value market is vital.

Commercialising a new therapy is a very lengthy and expensive process, encompassing a pre-clinical phase (proof of concept), followed by three clinical phases during which safety and

efficacy tests are conducted on humans, a (pre)registration phase when the result of clinical trials are scrutinized by regulatory agencies, and in some cases a fourth round of clinical trials after regulatory approval has been granted. Such process can last for up to 12-15 years and cost up to $1.7 billion [2]. Our approach consists of estimating how many compounds a given firm is expected to move forward, across clinical phases, over a certain time period. By knowing the structure and composition of a portfolio of compounds at a certain point in time, we were able to estimate the structure and composition of the same portfolio at the end of a given period.

We interpreted this *expected portfolio* as reflecting the drug development performance of an *average* firm within a specified therapeutic area. We then compared a firm *expected* performance with its *actual* performance to ascertain its tendency to deviate from the *average performance of the area*. Based on the characteristics of firm *i*, with *i = 28* (large biopharmaceutical firms) drug development portfolios $\pi_{ti} = (\pi_{ti1}, \ldots, \pi_{ti13})$ (number of compounds under development in 13 therapeutic areas at time *t*, we estimate the transition probabilities across different phases. Then, for each firm we used such probabilities to calculate the *expected number* of *successful phase transitions*, over a defined time horizon, and based on this we computed the *expected portfolio* of compounds. At any time, the expected portfolio can be compared with the actual portfolio to measure firm *i's ability* to deviate from its *expected drug development performance*.

We believe this approach presents several advantages with respect to indicators that count inputs and/or outputs of the innovation process at specific points in time. To begin with, it allows assessing performance over a given time period, offering the opportunity to detect changes that take place within such period as well as across different periods. Secondly, it can be adjusted and calibrated to implement sensitivity analysis. Thirdly, it allows monitoring and assessing the behaviour of biotech and pharmaceutical companies throughout all clinical phases and therapeutic areas. Finally, while it provides a benchmark to compare the performance of different firms, it could potentially be employed for alternative purposes, such as assessing the consequences of an increase in the number of compounds that progress from pre-clinical to clinical and/or a change in the success probabilities assigned to such transitions.

3. MEASURING DRUG DEVELOPMENT PERFOMANCE

The analysis aims at considering two key features of a firm performance: the number of registered drugs and compounds in each phase, and the time at which such phases are reached. Indeed, although the number of registrations is an obvious indicator of performance, time of registration is also very important, as confirmed by the introduction of regulatory changes such as the *US Fast Track Development Program* [19] or the *Priority Review Vouchers* [20].

3.1 Data Collection Procedure

To build and test our model we collected data from *Biopharm Insights*. We first estimated the average duration of each clinical phase (table 1) within thirteen therapeutic areas (tables 1-2) by computing the average length of the clinical trials. The period covered was January 2000 to December 2009. Trials were selected for which we could identify both the start and the end date. We grouped together clinical trials exhibiting the same (i) indication; (ii) therapeutic area (iii) trial design and (vi) clinical phase. As a result of these selection criteria, out of 9646 successfully completed clinical trials we selected 7616 'cluster of trials' (79%).

INSERT TABLE 1 ABOUT HERE

Second, we estimated attrition and success rates for each therapeutic area. When a phase was

successfully completed, but lasted for longer than the average completion time, we classified it as a 'repeated phase'. We considered two time intervals: January 2000–December 2004 and January 2005-December 2009. Data from the period 2000-2004 were used to estimate the probabilities of success, failure (probability of termination) and phase repetition (probability that a trial was extended beyond the average duration), which we then used to forecast the *average portfolio performance* at December 2009[i]. For each therapeutic area, table 1 shows the estimated transition probabilities. These data exhibit some clear differences as compared to other works [2] [5] and [7] due to the methodology for data selection, the consideration of all clinical studies and not only approved drugs, the decision to distinguish among successful, failed and repeated phases, and a higher degree of data disaggregation concerning therapeutic areas.

Third, using the *Biopharm Insights* database we estimated the drug development portfolio (including the pre-clinical and discovery phases) of twenty-eight companies at 31/12/2009. Our sample includes biotechnology companies with at least ten therapeutic compounds in the pipeline, 250 employees, and $100ml in turnover at 31/12/2009.

Finally, we counted the number of investigational drugs that completed phase 3 and entered/completed a procedure for approval in the January 2005-December 2009 period.

3.2 The Model Framework

In the analysis we consider each therapeutic area separately, modelling its dynamics as a time-discrete dynamic process with time-invariant transition probabilities. For each therapeutic area, the number of compounds in each clinical phase defines the *state* of the *system*.

Figure 1: Model representation

INSERT FIGURE 1 ABOUT HERE

Given the average time length of each development phase, the total number of compounds in a phase is defined by the sum of (i) compounds outsourced from other organisations or stemming from pre-clinical research, (ii) compounds that successfully completed the previous clinical phase, and (iii) compounds repeating the same phase, that is with a development time longer than the average time length. We excluded those compounds failing to complete the phase and quitting the pipeline (negative contribution).

Compounds successfully completing phase 3 are filed for approval, and eventually registered.

Figure 2: Subdivision of the generic phase i into sub-states.

INSERT FIGURE 2 ABOUT HERE

For each clinical phase $i = 1,2,3$ each sub-state is indicated by (i, j), meaning month j of phase i.

3.3 Simulating the portfolio performance

The model we built allows an arbitrary (though finite) number of entries and exits in each month. Based on the available data, we performed the following types of simulation. At the beginning of 2005, for each company we introduced as an input the 31/12/2004 portfolio, to simulate its evolution across the years until the end of the 2009, using as attrition rates the percentages displayed in table1. At the same time, each year we also took into account compounds in discovery and in the pre-clinical phase. These compounds were introduced in the portfolio by assuming an average probability equal to 0.7. Such probability, of successful transition from pre-clinical to clinical phases was originally suggested by [7], and a similar value was identified by [2]. We also considered compounds that entered the pipeline via in-licensing, alliances, mergers and

acquisitions (M&A).

Hence, for each firm *i = 1…28*, we calculated $E\pi_{2009i}$, the expected number of compounds in its portfolio, which estimated the firm pipeline at date 31/12/2009, based on the average duration of clinical phases and the average probability of phase success, failure and repetition, for each therapeutic area. Then we computed the difference $y_{2009i} = \pi_{2009i} - E\pi_{2009i}$ to obtain a measure of firm *i's* performance against the industry average, within each therapeutic area.

3.4. Results

For each firm *i*, and each therapeutic area, table 2 show the values of $y_{2009i} = \pi_{2009i} - E\pi_{2009i}$.

INSERT TABLE 2 ABOUT HERE

Despite the potential limitations of the findings, related to our assumptions, these results provide some general insights on the (relative) performance of the twenty-height companies. For instance, our cumulative results in the area of *cancer* show that most companies (with some notable exceptions) outperformed the model predictions. This suggests that performance (in the January 2005-December 2009 period) has generally improved in this area, a finding that might be explained in more than one way, including the fact that regulatory measures such as the *Orphan Drug Act (*ODA) may have incentivised R&D effort in cancer. Within our sample, it resulted in more rapid progression than expected; this is consistent with [5] who calculate time duration over the 1990-99 and 2000-2009 periods. As shown by [21], since 1982 the therapeutic area of cancer has seen the highest concentration of clinical studies under the ODA. Moreover [2], [6] and [9] suggest that the ODA can have a major impact on the expected revenues of a biopharmaceutical firm and, as a direct consequence, on its incentive to invest in this area.

4. DRUG DEVELOPMENT PERFORMANCE: DETERMINANTS AND CONSEQUENCES

We used these results (table 3) to investigate the relationship between drug development performance and per-capita revenue growth. We began by building two indicators of innovative performance for each firm, measuring the deviation of firm *i's* portfolio from the expected performance, normalised by the maximum deviation within each therapeutic area over the 2005-2009 period and the total number of compounds in each portfolio. The former reflects the different intensity at which innovative performance fluctuates across therapeutic areas (table 2), deviation patterns being more pronounced in the case of *cancer*. We mitigated this effect by normalising our indicator using $[Max_i[y]_{2009i} = \pi_{2009i} - E\pi_{2009i}]$ for each area. The latter type of normalisation is motivated by the fact that companies in our sample differed in terms of their portfolio structure and size.

Studies investigating the relationship among technological abilities, innovative and financial performance, rely on various measures of financial success. For instance, while [22] draws attention to indicators of returns on sales-assets-equities and economic added value, [23] suggests focusing upon returns on investments, as a measure of revenue growth that directly reflects the impact of launching new products. The introduction of a new good, or service, at time *t* is reflected in the change in sales revenues at time *t+k*. In this article, the indicators of drug development performance reflect the cumulative deviation of each firm over the period January 2005-December 2009, while our indicators of financial performance reflect per-capita variation over the period January 2006-December 2010 (table 3).

Our decision was motivated by the fact that, with specific reference to the firms in our sample, moving compounds through subsequent clinical phases can have an immediate effect on financial

performance. That is, a drug receiving regulatory approval at time *t*, with *t = 2005…2009*, can already generate revenues at time *t+1*. Furthermore, because discovery and development of new treatments can last for many years, and fragmentation of activities is increasingly shaping the industry's value chain, it is important to observe that inventions in this field are likely to become economically valuable long before a new drug is approved and/or commercialised [3] [24].

As argued in [2] and [25], the debate around the link between innovative and financial performance hinges on the ability to reduce attrition rates, development costs and time-lines. This ability is related to three broad types of factors. First, regulatory factors act as either incentives or barriers to invest in drug development activities [26]. Works like [17] and [27] focus on price regulation, [1], [8], [4], [9], [19] and [21] on regulatory changes such as the ODA, while [16] sheds light on the effects of the increasing regulatory requirements for clinical trials.

Second, science and technology-related factors can also be critical. For instance, radical innovation is often associated to the concept of *first-in-class* therapies. Incremental innovation instead denotes improvements of drug effectiveness or reduced toxicity. Developing first-in-class drugs often entails higher risk for a firm, with no guarantee of obtaining the top earning product.

Third, firm-level factors related to strategic decision-making are also frequently considered as affecting innovative performance. Many authors refer to the extent to which biopharmaceutical firms rely upon external sources of knowledge, and their ability to manage knowledge(s) internally, as key success factors.

Strategic alliances are seen as an important route to profitability. From the viewpoint of incumbent PCs, upstream alliances tend to be motivated by the need to strengthen R&D activities, explore new research avenues and diversify portfolios reducing fixed costs. For both PCs and biopharmaceutical firms, downstream alliances are more oriented towards exploitation of achieved results as well as to create safer and faster routes to market. Both in-licensing and M&A can also provide the immediate advantage of filling drying pipelines and getting direct access to intellectual assets [15]. However, rather than implementing M&A, retaining internal absorptive and exploitation capacity, promoting the creativity of highly-focused research units, and dealing with diseconomies of scale is often seen as critical to successful innovation. As suggested by [18], the firm capabilities defined in millions USD invested each year in specific therapeutic areas and a measure of experience-based economies of scope, quantified by an *Herfindahl-Hirschman Index* (HHI), contribute to capture innovative performance. Similarly, works such as [16] argue that R&D scope and scale can affect the firm's ability to select promising compounds and complete drug development.

Our main focus is on strategic factors and the proportion of biological compounds in a drug R&D portfolio (table 3). We initially tested (table 4, Model 1) the impact of a number of variables on per-capita revenues variation, including experience-based scope economies (i.e. HHI), the spread overtime (2005-2009) of R&D investments across therapeutic areas, the proportion of biological compounds, and our indicator of drug development performance in each clinical phase normalised with respect to the highest number compounds in each therapeutic area. Then, in Model 2 (table 4) we investigated the impact of HHI, spread of R&D investment, proportion of biologicals, and firm size on each indicator of drug development performance[ii].

INSERT TABLES 3-4 ABOUT HERE

To begin with our results highlight the key role played by a firm ability to deviate in clinical phase 3 from its expected performance in explaining financial performance. More precisely, the higher a firm ability to deviate, as normalised with respect to the best performance in each therapeutic area, the greatest its revenue growth. The effect of the relative deviation in other clinical phases

is not statistically significant. We think this may be due to the long time required to complete phases 1 and 2 and to introduce an approved drug into the market, a particularly problematic issue in our analysis since deviations are computed over the period 2005-2009 and revenues growth over the period 2006-2010.

A positive and significant correlation exists between both the measure of experienced-based economies *of scope* (HHI) and spread over time of R&D investment across therapeutic areas and per-capita revenue growth. This suggests that accumulating experience in NDA filing within a therapeutic area, and obtaining phase 3 approvals for drugs together with the development of marketing capacity and distribution channels can lead to stronger financial performance, provided these activities are implemented in the relevant therapeutic areas. In other words, targeted R&D efforts alongside the accumulation of competence in marketing and distributing new drugs can enable a company to exploit economies of scope across other indications, but only within a limited number of therapeutic areas. In this sense, our findings can be considered in line with [28], who argues that scale in sales and marketing tends to be associated with clear financial advantages.

Model 2 shows that deviation ability in phase 2 contributes to explain innovative performance in phase 3, suggesting that large biopharmaceutical companies are not mere exploiters of outsourced compounds. Furthermore, HHI is negatively related to drug development performance (especially in phase 3), which suggests that a portfolio focusing on a restricted number of therapeutic areas could negatively impact on the probability of taking a drug through to the market stage. However, the relationship is not statistically significant and further doubts about this result are raised by the positive and high correlation between a firm's ability to deviate in phase 2 and R&D investment over time, across therapeutic areas.

Finally, consistently with [28], we find that a higher proportion of biologicals in a portfolio (BIO) tend to deliver a better financial performance. Often, this is because (i) patents that took many years of research are more difficult to imitate and infringe and (ii) a number of biologicals target diseases affecting small populations, which reduces the number of patients involved in clinical trials (for instance this is the case with *stratified medicine*) and allows avoiding crowded markets [5].

INSERT TABLE 5 ABOUT HERE

The results we obtained in Model 3[iii] (table 5) are similar to Models 1, showing that our approach in not sensitive to the kinds of normalisation adopted.

5. CONCLUSIONS

This article proposes a new approach to assess the drug development performance of firms developing treatments for healthcare. Our work was motivated by some dissatisfaction with the existing measures of innovative input/output, as we felt they would not provide a dynamic assessment of performance over long periods of time or a proper view on uncertainty in attrition and phase duration, across therapeutic areas. We believe our approach goes some way towards achieving the above goals. First, it provides an overview of firms' ability (or inability) to outperform the industry average and an evaluation of the relative performance of the firms included in our study. Then, it identifies possible similarities and divergences in firm-level performance across different therapeutic areas (tables 2-3). One of the merits of our approach rests with its wide scope for application, as in testing the effect of regulatory, organizational and strategic changes intended to improve drug development performance on certain sets of companies. For instance, in spite of the relatively long lead-times in therapeutic areas such as

c*ancer* (table1), concentration of investments in this area, which may be the result of regulatory changes [9] [19], seems to have had an impact on large biopharmaceutical companies' ability to outperform the industry's average (table 2).

Our main intuition was that financial performance may depend not only on the ability to bring new drugs to the market, but also on doing it faster than competitors. The results presented in this article are consistent with such intuition, especially when a firm drug development performance is measured by the extent to which it outperforms the industry average in clinical phase 3. Such result may be partly explained by the fact that our sample includes twenty-eight (subsequently reduced to twenty-five) large biopharmaceutical firms, most of which are capable of getting compounds approved and marketed. We cannot exclude that a larger sample, with smaller and non-vertically integrated firms, might lead to different results, perhaps highlighting the impact of commercial strategies based on the out-licensing of early-stage clinical programs.

Nonetheless, our findings also provide interesting clues about the impact of strategic decisions concerning the allocation of R&D investments, with an emphasis on the effect of scale/scope economies concerning therapeutic areas. We detect a correlation between the ability to complete clinical phase 3 and financial performance, suggesting that the business model of big biopharmaceutical companies may be more similar to the one of PCs than smaller biotechnology companies. However, we also find that the concentration of R&D investments, in a restricted number of areas, is positively related to financial performance. Thirdly, a correlation exists in our data between ability to complete clinical phases 2 (conducted in a relatively small number of patients) and 3. As works such as [4] suggest that biotechnology companies have been more effective R&D investors than PCs, all together these results suggest that the companies in our sample could be regarded as a *raw organisational model* for the entire industry. Indeed, many of them have now been acquired by PCs, albeit preserving their managerial and R&D efficiency often remained a key strategic priority.

We conclude observing that companies with a significant proportion of biological compounds in their portfolios tend to have a better drug development, and financial, performance. A possible explanation for this could be that *rational drug design* [10] helps reducing attrition rates, since candidate molecules are initially selected with the right properties in mind. Also, on average biologicals are more likely, than chemical entities, to target diseases for which regulatory measures have been relaxed as well as unexploited and/or less competitive therapeutic indications [28].

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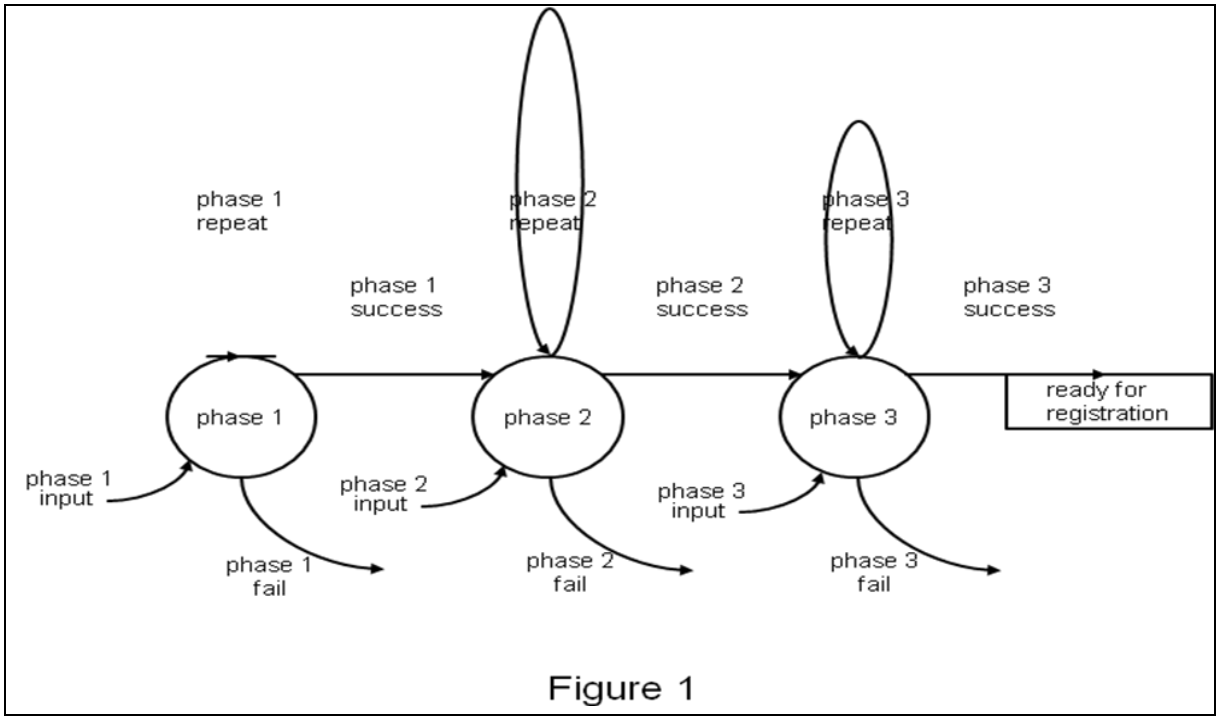

Figure 1

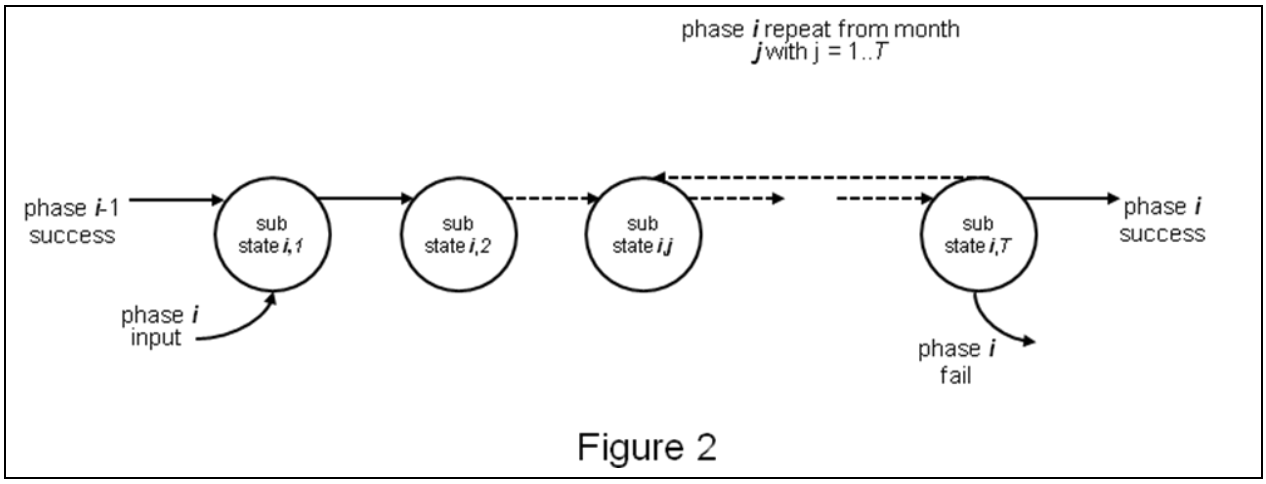

Figure 2

TABLE 1

	phase	average phase duration (months)	P_{fail}	P_{repeat}	$P_{success}$
Cancer	ph 1	24.0	38.0	41.0	21.0
	ph 2	33.6	29.0	36.0	35.0
	ph 3	38.4	35.0	27.0	38.0
Cardiovascular	ph 1	11.2	37.0	43.0	20.0
	ph 2	19.9	17.0	48.0	35.0
	ph 3	28.2	20.0	39.0	41.0
CNS	ph 1	9.5	35.0	37.0	28.0
	ph 2	21.1	17.0	55.0	28.0
	ph 3	25.4	17.0	45.0	38.0
Dermatology	ph 1	9.4	15.0	70.0	15.0
	ph 2	16.6	17.0	45.5	37.5
	ph 3	20.1	3.0	36.0	61.0
Gastrointestinal	ph 1	10.1	38.0	31.0	31.0
	ph 2	20.1	22.0	32.0	46.0
	ph 3	27.5	30.0	31.0	39.0
Genitourinary	ph 1	9.1	27.0	26.0	47.0
	ph 2	23.6	18.0	46.0	36.0
	ph 3	28.1	17.0	39.0	44.0
Hematological	ph 1	27.7	25.0	41.0	34.0
	ph 2	30.1	28.0	38.0	34.0
	ph 3	27.1	15.0	46.0	39.0
Hormonal System	ph 1	9.5	23.0	60.0	17.0
	ph 2	14.4	19.0	47.0	34.0
	ph 3	27.5	20.0	50.0	30.0
Immune System	ph 1	12.2	43.0	43.0	14.0
	ph 2	19.9	24.0	45.0	31.0
	ph 3	20.2	28.0	24.0	48.0
Infectious Diseases	ph 1	12.5	18.0	52.0	30.0
	ph 2	19.6	34.0	36.0	25.0
	ph 3	23.1	18.0	52.0	30.0
Pain	ph 1	8.0	18.0	46.0	36.0
	ph 2	13.9	12.0	52.0	36.0
	ph 3	22.9	11.0	37.0	52.0
Musculoskeletal	ph 1	16.8	20.0	35.0	45.0
	ph 2	18.9	24.0	35.0	41.0
	ph 3	20.2	25.0	42.0	33.0
Respiratory	ph 1	11.7	24.0	38.0	38.0
	ph 2	15.5	14.0	55.0	31.0
	ph 3	21.7	11.0	49.0	40.0

TABLE 2

PU_{2009i}-EU_{2009i}	cancer	cardio	cns	derma	gastro	geno	hema	hormo	immu	infe	pain	musco	resp
AMGEN	2	-1	-1	-1	-1	0	0	-1	-2	0	-1	0	-1
AMYLIN	0	-1	0	-1	0	0	0	3	0	0	0	-1	0
BIOGEN	3	4	-1	1	0	0	0	0	-1	-1	0	0	0
CELGENE	2	0	0	0	-1	0	1	0	-2	0	0	-1	0
CENTOCOR	2	-1	0	2	0	0	0	0	-1	0	0	1	0
CEPHALON	2	0	3	0	0	0	0	0	0	0	4	0	0
CUBIST	0	0	0	0	0	0	0	0	0	2	0	0	0
ELAN	0	-1	3	0	1	0	0	0	0	1	0	1	0
ALLERGAN	-1	0	2	1	0	2	0	0	1	1	2	0	0
ENZON	0	0	0	0	0	0	0	0	0	1	0	0	-1
EXELIXIS	0	-1	-1	0	0	0	0	-1	-1	0	0	0	0
GENENTECH	3	0	0	0	-1	0	0	1	-1	-1	-1	0	0
GENZYME	5	-1	0	1	-1	0	-1	2	-3	1	-1	-1	-1
IMCLONE	1	0	0	0	0	0	0	0	0	0	0	0	0
MEDIMMUNE	0	0	0	-1	-1	0	-1	0	-3	2	0	-1	0
MERCK	1	2	-2	-1	-1	3	0	-1	-1	1	0	0	0
MYRIAD	6	0	1	0	-1	0	0	0	0	0	-1	1	-1
QLT	0	0	0	-1	0	0	0	0	-1	-1	0	0	0
REGENERON	0	1	-1	0	-1	0	0	0	-1	0	0	1	0
TALECRIS	0	0	0	0	0	0	1	-1	2	0	0	0	1
UNITED	0	4	1	0	0	0	0	1	-1	1	1	0	0
VERTEX	0	-1	-1	-1	0	0	0	0	-1	1	0	-1	0
ALKERMES	0	0	0	0	0	-1	0	1	-1	0	0	0	0
ANLYLAM	0	0	0	0	0	0	0	0	0	0	0	0	0
ALEXION	0	2	-1	-1	-1	0	0	-1	-1	0	0	-1	0
INTERMUNE	0	0	0	0	0	0	0	2	0	0	0	0	0
ISIS	0	-1	0	-2	-1	0	0	2	0	-1	1	0	0
SALIX	0	0	0	0	4	0	0	0	-1	0	0	-1	-1

TABLE 3

Dependent variable:

1- **Revenues growth per employee (2006-2010)**:

$$\frac{[Revenues_{2010i} - Revenues_{2006i}]}{Total\ number\ of\ employees\ for\ firm\ i\ at\ time\ t = 2006}$$

where *r*evenues are expressed in *Million USD.*

Independent variables:

1- **Ability to deviate in each phase transition**

$$\frac{[\pi_{2009ij} - E\pi_{2009ij}]}{(|Max_i|\pi|_{2009ij} - E\pi_{2009ij}|)}$$

in each therapeutic area, where π_{2009ij} is the number of compounds recorded in December *2009,* $E^{E\pi_{2009ij}}$ the expected number of compounds one, and $j = 1,2,3$ indicates the clinical phase.

2- **The firm's Size**: Total Number of Employees (f

3- **Herfindahl-Hirschman Index (HHI)** (economie

Normalised with respect to:
- maximum deviation within therapeutic area
- total compounds developed by each firm

For each firm $i = 1,..,25$ is given by

$$HHI_i = \sum_{j=1}^{13} \pi_{2009ij}^2$$

4- **Change over time in R&D spread across therapeutic areas**:

$$\frac{[R\&D_{2009i} - R\&D_{2005i}]}{Number\ of\ therapeutic\ areas\ in\ which\ firm\ i\ is\ active\ at\ t = 2009}$$

5- **BIO**:

$$\frac{Number\ of\ biological\ compounds\ for\ firm\ i\ at\ t = 2009}{Number\ of\ chemical\ compounds\ for\ firm\ i\ at\ t = 2009}$$

Note that: Index i will refer to the firm, with $i = 1,..,25$

Table 4: Regression Models 1 – 2

MODEL 1 - INDEPENDENT VARIABLE: Revenue growth per employee (2006-2010)						
DEPENDENT VARIABLES	**Coefficient**	**Std. Error**	**T-stat**	**P>t**	**95% Confidence Interval**	
Change R&D Spread	0.9237907	0.4785215	1.93	0.068	-.0743874	1.92196
HHI	110.3533	56.21752	1.96	0.064	-6.914391	227.621
BIO	107.2646	51.0375	2.10	0.048	.8022553	213.727
Deviation Phase 3	330.5004	185.1565	1.78	0.089	-55.72938	716.730
Constant	46.47229	48.09237	-0.97	0.345	146.7912	-53.8466
Number of obs	25		F(4, 20)	3.27		
Prob > F	0.0324		R-squared	0.3992		
Adj R-squared	0.2743		Root MSE	74.038		
Note that: DEV-Ph1/2_MX and SIZE have been dropped because they were not statistically significant						
MODEL 2 - INDEPENDENT VARIABLE: Deviation Phase3						
DEPENDENT VARIABLES	**Coefficient**	**Std. Error**	**T-stat**	**P>t**	**95% Confidence Interval**	
Deviation Phase 2	0.3723973	0.1524495	2.44	0.023	0.0562363	0.6885582
HHI	-0.0990449	0.0692056	-1.43	0.166	-0.242568	0.0444786
Constant	0.1411145	0.04211	3.35	0.003	0.0537837	0.2284453
Number of obs	25		F(2, 22)	4.82		
Prob > F	0.0184		R-squared	0.3047		
Adj R-squared	0.2415		Root MSE	.39493		
Note that: DEV-Ph1_MX BIO, RD_TA and Size have been dropped because they were not statistically significant						

Table 5: Regression Model 3

MODEL 3 - DEPENDENT VARIABLE: Revenue growth per employee (2006-2010)						
DEPENDENT VARIABLES	**Coefficient Robust**	**Std. Error**	**T-stat**	**P>t**	**95% Confidence Interval**	
Change R&D spread	1.2606	0.4672232	2.70	0.014	0.2860351	2.2352
HHI	137.5516	48.24703	2.85	0.010	36.91005	238.1931
BIO	166.5349	69.34919	2.40	0.026	21.87506	311.1948
Deviation Phase 3	90.7212	29.42575	3.08	0.006	29.34018	152.102
CONSTANT	-107.5269	56.27525	-1.91	0.070	-224.915	9.86123
Number of obs	25		F(4, 20)	4.52		
Prob > F	0.0092		R-squared	0.4465		
Root MSE	70.832		Root MSE	70.832		
Breusch-Pagan / Cook-Weisberg test for heteroskedasticity						
HO	Constant variance		Variables	Fitted value of RPE_610		
chi2(1)	5.79		Prob > chi2	0.0161		

[i] The different probabilities can vary as to whether or not we include trials for which end date is known. The probability of completion tends to be higher if we include only trials/phases for which the date of completion is known. However, this is not always the case when we consider specific combinations of therapeutic area/clinical phase. NCI is responsible for the overwhelming majority of missing data. Since in this work we are mostly concerned with trials/phases conducted by private companies (whether or not in collaboration with public research organisations) and most of the reported trials conducted by the NCI do not involve collaborations with private companies, then the bias in the results due to missing observations is reduced.

[ii] We ran OLS regressions and excluded 3 firms from the analysis for which financial information was not available. We checked for reversed causality, endogeneity and multicollinearity, and found that none of them applies. The endogeneity test was performed by calculating residuals from an equation where phase 3 deviation is the dependent variable; then a new regression with revenues growth per capita as a dependent variable was run in which the first-stage residuals were included as independent variables. Finally, a t-test performed on the coefficient of those residuals showed that they are not statistically significant. Correlation coefficients suggested multicollinearity is not a problem. Disturbances are not heteroskedastically distributed.

[iii] Because disturbances are heteroskedastically distributed, we ran our analysis by employing robust standard-errors.